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(54) Title: NON-TABLETTED, CHEWABLE, INDIVIDUALLY DOSED ADMINISTRATION FORMS

(57) Abstract: The invention relates to individually dosed administration forms for pharmaceutically active compounds, consisting of non-tabletted, chewable gel compositions packaged in blisters or cavities; to a process for the manufacture of such individually dosed administrationforms; to individually dosed administration forms obtainable by the abovementioned process; and to the use of a stabilisingagent to enhance the ease of removal of the composition from the blisters or cavities.

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NON-TABLETTED, CHEWABLE, INDIVIDUALLY DOSED ADMINISTRATION FORMS

The invention relates to individually dosed administration forms for pharmaceutically active compounds, consisting of non-tabletted, chewable gel compositions packaged in blisters or cavities; to a process for the manufacture of such individually dosed administration forms; to individually dosed administration forms obtainable by the above-mentioned process; and to the use of a stabilising agent to enhance the ease of removal of the composition from the blisters or cavities.

Chewable delivery systems, such as chewing gums, are highly desirable means for the oral administration of pharmaceutically active compounds. A disadvantage of chewing gum compositions is that they generally include a water insoluble gum base, which remains in the mouth and must be disposed of. In addition, many active compounds may have affinity for the gum base, making thus accurate dosing difficult.

British Patent application GB 2 009 597 discloses chewable and swallowable, gelled antacid compositions. The compositions are obtained by dispersing an antacid in a solution comprising water, a carbohydrate or a polyhydric alcohol as a bodying agent and an amount of gelling agent sufficient to cause the liquid dispersion to set to a self-supporting gel after cooling. In a preferred embodiment the still liquid dispersion can be poured before cooling into oral unit dosage moulds and allowed to set.

This process no longer requires separate shaping and packaging of solid administration forms. These are given their particular shape during the packaging operation by simple application of the softened composition into a substrate with the desired shape, followed by solidification. This results in an improved cost efficiency of the overall manufacturing process.

International patent application WO 87/00429 describes opacified gelatine

compositions and processes for their manufacture. The compositions comprise fats, fatty oils or fat derivatives to improve the light stability of the dyes used to colour the gelatine compositions. The specification states that all fats, fatty oils or fat derivatives of synthetic or natural origin, as well as partially hydrogenated products can be used, provided that they are physiologically safe.

It has now been found by the inventors that the use of gelatine as a gelling agent for the manufacture of non-tabletted, chewable compositions as those described in the prior art yields compositions that, upon ageing, do often present the problem that they cannot be easily removed from the packaging where they have been shaped without leaving residues in the packaging. The problem of residues left in the packaging upon removal of the jelly composition is particularly pronounced when the shape of the packaging shows edges or portions with a small radius of curvature.

The inventors have solved this problem by incorporating into a matrix material, comprising a mixture comprising a gelatine at least one water-soluble alcohol and/or water as a solvent and at least one stabilising agent selected from the group consisting of esters of glycerine and fatty acids and products resulting from the alcoholysis / esterification reaction of such esters of glycerine and fatty acids with polyethyleneglycols, the stabilising agent having a melting point in the range of 42° C to 63° C. This results in non-tabletted, individually dosed administration forms comprising a composition of at least one pharmaceutically active substance dissolved or dispersed within the matrix material, which composition is plastic at elevated temperature. These administration forms can be removed from the packaging without leaving residues. In a preferred embodiment of the present invention only one stabilising agent is incorporated into the matrix material.

As essential ingredients the composition of the present invention comprises at least one pharmaceutically active substance, gelatine present in an amount of at least 0,2% by weight of the composition, at least one stabilising agent as described above, and at

least one water-soluble alcohol and/or water as a solvent, wherein water is present in an amount not greater than 46% by weight of the composition. It may also comprise bodying agents that impart texture and body to the final gel, and other optional components such as preservatives, antioxidants, defoaming agents, sweeteners, taste-masking agents, colour and flavours. It is a preferred embodiment of the present invention that only one stabilising agent is used.

The bodying agents suitable for the present invention are sugars such as glucose, sucrose and fructose, sugar alcohols such as sorbitol, mannitol and maltitol and polysaccharides such as starch, cellulose and functionalised cellulose derivatives.

To ensure consumer acceptability it is preferred that the non-tabletted, individually dosed administration forms of the present invention have compositions showing no plastic deformation at temperatures below 37°C.

Gelatine is a protein obtained by extraction from animal raw materials containing collagen such as skins and bones, which have been previously conditioned by acidic or alkaline treatment. Commercially available gelatine typically contains 84-92% protein, 0,1-2% salts and the rest is water.

Commercially available gelatines are classified according to the raw material from which they have been obtained and according to their ability to gel, which is customarily measured as Bloom gel strength.

Although all types of gelatine can be used for the manufacture of the individually dosed administration forms of the present invention, it has been found that gelatines with a Bloom range comprised between 140 and 270 degrees Bloom, preferably between 180 and 250 degrees Bloom yield composition with optimum consumer acceptance in terms of palatability. Gelatines obtained though alkaline treatment are in general preferred to those obtained through acidic treatment.

It is preferred that the compositions of the present invention comprise gelatine in an amount greater than 0,2% by weight of the composition, more preferably greater than 1% by weight and still more preferably greater than 5% by weight of the composition.

The stabilising agent of the present invention is selected from the group consisting of esters of glycerine and fatty acids and products resulting from the alcoholysis / esterification reaction of such esters of glycerine and fatty acids with polyethyleneglycols having a melting point in the range of 42° C to 63° C.

Examples of such stabilising agents are the mono-, di- and triesters of glycerine with fatty acids and mixtures thereof, preferably the diesters of glycerine with fatty acids. Preferred fatty acids are those selected from C10-C20, preferably C16-C18, unsaturated, saturated fatty acids. Examples of such fatty acids are lauric, oleic, linoleic, linolenic, palmitic and stearic acids. An example of a preferred commercially available ester is Estol ® 3745 GDS T2 from Uniqema. Other examples of stabilising agents are the products of the alcoholysis/esterification reaction of the esters of glycerine and fatty acids mentioned above. Preferred examples are products of the alcoholysis/esterification reaction of hydrogenated palm kernel oil or hydrogenated palm oil with PEG 1500, such as Gelucire ® 44/14 and Gelucire ® 50/13 from Gattefossé.

In an embodiment of the invention the solvent or solvents present in the composition is/are used in a total amount greater than 10% by weight, more preferably greater than 25% by weight still more preferably greater than 50% by weight of the composition.

In another embodiment of the present invention the amount of water of the present compositions is not greater than 46% by weight, preferably not greater than 35% by weight, most preferably not greater than 25% by weight, most preferably not greater than 15% by weight of the composition.

The compositions of the present invention comprise at least one pharmaceutically active substance which is dispersed or dissolved within the matrix material when it is in the molten state. The pharmaceutically active substance need not be in any specific form for its successful incorporation within the molten matrix material, in particular it is not required, and also not preferred, that the pharmaceutically active substance is provided as a component of a shearform matrix carrier prepared by flashflow processing.

Suitable pharmaceutically active substances that may be contained in the individually dosed administration forms of the present invention vary widely and generally represent any stable drug combination. Illustrative categories and specific examples include:

a) ANTACIDS:

i) Inorganic or organic salts of aluminium, for example, aluminium allantoinate, aluminium aminoacetate, aluminium phosphate, aluminium silicate, aluminium glucoheptanoate or aluminium polygalacturonate.

ii) Inorganic or organic salts of bismuth, for example, bismuth aluminate, bismuth carbonate, bismuth silicate, bismuth subcarbonate or bismuth citrate.

iii) Inorganic or organic salts of calcium, for example, calcium phosphate or calcium aminoacetate.

iv) Inorganic or organic salts of magnesium, for example, magnesium carbonate, basic magnesium carbonate, magnesium phosphate or magnesium silicate.

v) Oxides and hydroxides, such as aluminium oxide, algeldrate (aluminium hydroxide), magnesium or calcium oxides or hydroxides.

vi) Mixed salts of aluminium and sodium as silicate, mixed salts of aluminium and magnesium as hydrotalcite (basic aluminium and magnesium carbonate), almagate (basic aluminium and magnesium carbonate) or magaldrate (basic aluminium and magnesium sulphate), mixed salts of bismuth and magnesium as magnesium silicate,

and magnesium aluminosilicates, as simaldrate or almasilate.

vii) Hydrogen carbonates as sodium or potassium hydrogen carbonates.

viii) Glycine.

ix) Alginic acid and salts thereof.

and mixtures thereof.

b) DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX

Ranitidine*, Nizatidine, Famotidine, Cimetidine, Roxatidine, Pifatidine, Roxatidine, Sufotidine, Lafutidine, Osutidine, Pantoprazole, Omeprazole, Lansoprazole, Esomeprazole, Rabeprazole, Esaprazole, Pariprazole, Aripiprazole, Leminoprazole, Amoxicillin, Trospectomycin, Clarithromycin, Zinc Acexamate, Cetraxate, Rotraxate, Dosmalfate, Flavalfate, Sucralfate, Bismuth salts as bismuth citrate or subsalicylate, Triletide, Dicloguamine, Sulfoxazine, Rioprostil, Ritipenem, Trimoprostil, Benexate, Pramipide, Misoprostol, Alaptide, Proglumide, Azuletil, Trepenone, Polycnephosphatidylcholine, Plaunotol, Troxipide, Midoriamine, Ecabet, Quinotolast, Sulglicotide, Nitazoxanide, Revaprazan, and mixtures thereof.

c) DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS; PROPULSIVES

Metoclopramide, Cinitapride, Clebopride, Cisapride, Zacopride, Mosapride, Itopride, Prucalopride, Domperidone, Ecabapide, Polycarbophil calcium, Tegaserod, and mixtures thereof.

d) LAXATIVES

Sennatin, Sennosides A + B, Glycerol, Picosulfate, Lactitol, Bisacodyl, Polyethylene glycol, Lactulose, Basic magnesium carbonate, and mixtures thereof.

e) ANTIOBESITY PRODUCTS

Orlistat, Amfebutamone, Bupropion, Diethylpropion, Sibutramine, Fluoxetine,

Metaraminol, Mazindol, Chorionic gonadotrophin, Phentermine, Metamfetamine, Phendimetrazine, Benzfetamine, Phenylpropanolamine, Fenproporex, and mixtures thereof.

f) DIGESTIVES; ENZIME PREPARATIONS

Amilase, Cellulase, Lactase, Lipase, and mixtures thereof.

g) VITAMINES

Mixtures of vitamines, mixtures of oligoelements, and mixtures thereof.

h) APPETITE STIMULANTS

Pizotifen, Cryptoheptadine, Carnitine, Stolimine, and mixtures thereof.

i) ANTITHROMBOTIC AGENTS; PLATELET AGGREGATION INHIBITORS

Ditazole, Acetylsalicylic acid, Trifusal, Epoprostenol, Eptifibatide, Heparin, Clopidrogel, Dipyridamole, Abciximab, Ticlopirine, Dalteparin, Danaparoid, Warfarin, Phenindione, Dicoumarol, Epoprostenol, Enoxaparin, Nadroparin, Antithrombin III, Indobufen, Parnaparin, Tinzaparin, Dermatan, Desirudin, Reviparin, Thombomoduline, Bivalirudin, Ardeparin, Lepirudin, Tifacogin, Fondaparine, Fenprocumone, Certoparin, Bemiparin, Idraparinux, Acenocoumarol, Gabexate, Sulodexide, Defibrotide, Isbogrel, Cilostazol, Ciprostene, Ataprost, Sulotroban, Taprostene, Cloricromen, Picotamide, Alprostadil, Sulfinpyrazone, Beraprost, Daltroban, Variprost, Satrigel, Sarpogrelate, Tirofiban, Beraprost, Lamifiban, Lefradafiban, Xemilofiban, Polycosinol, Roxifiban, Lotrafiban, Sibrafiban, Alnidofibatide, Orbofiban, Argatroban, Ticlomarol, and mixtures thereof.

j) ANTIANEMIC PREPARATIONS; TRIVALENT IRON PREPARATIONS

Ferritine, Ferric proteine succinate, Ferric dextran and mixtures thereof.

k) ANTIARRHYTHMICS

Quinidine, Esmolol, Pirmenol, Acecainide, Pilsicainide, Recainam, Penticainide, Flecainide, Adenosine, Lidocain, Metoprolol, Propranolol, Nadolol, Oxprenolol, Phenytoin, Acebutolol, Sotalol, Carteolol, Medigoxine, Procainamide, Bretylium, Amiodarone, Disopyramide, Mexiletine, Moracizine, Tocainide, Propafenone, Barucainide, Alprenolol, Otenzepad, Verapamil, Diprafenone, Btacizin, Bidisomide, Arotinolol, Cibenzoline, Tiracizine, Pindolol, Diltiazem, Atenolol, Dofetilide, Tedisamil, Sematilide, Sotalol, Almokalant, Nifekalant, Ibutilide, Landiolol, Dronedarone, Talinolol, Tecadenoson, Digoxin, Indenolol, Prajmalium, Aprindine, Bunaftine, Butobendine, Lorajmine, Lorcainide, and mixtures thereof.

l) CARDIAC STIMULANTS, ORGANIC NITRATES

Isosorbide mononitrate or dinitrate, Nitroglycerol, Pentaerythrityl tetranitrate, Molsidomine, and mixtures thereof.

m) ANTIHYPERTENSIVES; ALPHA ADRENORECEPTOR ANTAGONISTS

Doxazosin, Urapidil, Nipradilol, Indoramin, Prazosin, Labetalol, Amosulalol, Terazosin, Monatepil, and mixtures thereof.

n) DIURETICS

Triamterene, Canrenoate, Spironolactone, Furosemide, Torasemide, Cicletanine, Piretanide, Chlorothiazide, Chlortalidone, Hydroflumethiazide, Bendroflumethiazide, Methyclothiazide, Polythiazide, Clopamide, Quinethazone, Bumetanide, Indapamide, Xipamide, Cyclopenthiazide, Canrenone, Docarpamine, Hydrochlorothiazide, Metolazone, Azosemide, Anaritide, Ularitide, Ecadotril, Candoxatril, Amiloride, Ethacrynic acid, Conivaptan, Telmisartan, Mebutizide, and mixtures thereof.

o) PERIPHERAL VASODILATORS

Dihydroergocristine, Piracetam, Nicergoline, Vinburnine, Cadralazine, Flunarizine, Metergoline, Hydralazine, Fasudil, Nicorandil, Linsidomine, Sildenafil, Cinnarizine,

Heptaminol, Almitrine, Raubasine, Pentoxifyline, Trimetazidine, Buflomedil, Alprostadil, Brovincamine, Cinepazet, Dilazep, Lidoflazine, Molsidomine, Nicorandil, Nifedipine, Trapidil, Viskenit, and mixtures thereof.

p) VASOPROTECTIVES

Diosmin, Hidroxmin, Hesperidin, Troxerutin, and mixtures thereof.

q) ANTIHYPERTENSIVES - SELECTIVE BETA BLOCKING AGENTS

Atenolol, Esmolol, Carteolol, Metoprolol, Bisoprolol, Carvedilol, Nebivolol, Propranolol, Tertatolol, Betaxolol, Cetamolol, Nipradilol, Tilisolol, Mepindolol, Nadolol, Oxprenolol, Acebutolol, Sotalol, Timolol, Labetalol, Penbutolol, Celiprolol, Amosulalol, Alprenolol, Cloranolol, Bopindolol, Soquinolol, Arotinolol, Pindolol, Talinolol, Esatenolol, Indenolol, Befunolol, Bevantolol, Bucomolome, Bunitrolol, Butofilolol, Carazolol, Lervonoprolol, Nifenalol, Rescimetol, Bunazosin, Doxazosin, Guanabenz, Guanadrel, Guanfacine, Guanoxabenz, Indoramine, Rilmenidine, Lofexidine, Naftopidil, Prazosin, and mixtures thereof.

r) SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS

Amlodipine, Nisoldipine, Nicardipine, Nitrendipine, Felodipine, Anipamil, Zonisamide, Benidipine, Darodipine, Tiapamil, Tetrandrine, Lercanidipine, Gallopamil, Bepridil, Diproteverine, Isradipine, Franidipine, Nivaldipine, Levetiracetam, Nimodipine, Verapamil, Aranidipine, Fasudil, Dotarizine, Lacidipine, Lomerizine, Cilnidipine, Nifedipine, Diltiazem, Paloridipine, Monatepil, Fantofarone, Semotiadil, Efenidipino, Manidipine, Barnidipine, Elgodipine, Pranidipine, Furaldipine, Ciclandelate, and mixtures thereof.

s) AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM; ACE INHIBITORS

Enalapril, Ramipril, Quinapril, Captopril, Perindopril, Fosinopril, Trandolapril, Cilazapril, Lisinopril, Spirapril, Moexipril, Delapril, Alacepril, Enalaprilat, Benazepril, Fentiapril, Zofenopril, Fosinoprilat, Utibapril, Temocapril, Ceranapril, Zofenoprilat, Imidapril, and mixtures thereof.

t) ANGIOTENSIN II ANTAGONISTS

Candesartan, Losartan, Eprosartan, Irbesartan, Valsartan, Tasosartan, Telmisartan, Olmesartan, and mixtures thereof.

u) CHOLESTEROL AND TRIGLYCERIDE REDUCERS

Atorvastatin, Lovastatin, Eptastatin, Simvastatin, Fluvastatin, Dalvastatin, Itavastatin, Rosuvastatin, Pravastatin, Probucol, Polycosanol, Ciprofibrate, Fenofibrate, Benzafibrate, Clofibrate, Filicol, Gemfibrozil, Benfluorex, Colestyramine, Phytosterols, Acipimox, Binifibrate, Clinofibrate, Colestilan, Diethylaminoethyl Dextran, Colestrol, Etiroxate, Etofibrate, Gugulipid, Meglutol, Melinamide, Niceritrol, Omacor, Pirifibrate, Sorbinicate, Sulodexide, Sultosilic Acid, and mixtures thereof.

v) ESTROGENS; FEMALE CONTRACEPTIVES

Estradiol, Ethinylestradiol, Norethisterone, and mixtures thereof.

w) DRUGS USED IN BENIGN PROSTATIC HYPERTROPHY

Pygeum Extract, Alfuzosin, Dutasteride, Finisteride, Oxendolone, Tamsulosin, and mixtures thereof.

x) CALCIUM HOMEOSTASIS; ANTIPARATHYROID HORMONES

Calcitonin, Elcatonin, and mixtures thereof.

y) ANTINEOPLASTIC AGENTS

Ameticine, Atrimustine, Diaziquone, Spiromustine, Melphalan, Elmustine,

Estramustine, Ranimustine, Dibromomulcitol, Tauromustine, Temozolomide, Carboplatin, Fotemustine, Aranose, Perfosfamide, Eptaplatin, Busulfan, Porfiromycin, Ifosfamide, Clorambucil, Altretamine, Cisplatin, Lomustine, Improsulfan, Mitobronitol, Mitolactol, Nedaplatin, Oxaliplatin, Prednimustine, Temozolomide, Treosuflan, Trofosfamide, Cyclophosphamide, Methotrexate, Butocin, Capecitabine, Carmofur, Cladribine, Cytarabine, Doxifluridine, Enocitabine, Fludarabine, Gemcitabine, Pentostatin, Raltitrexed, Tegafur, Etoposide, Pirarubicin, Aminoglutethimide, Anastrozole, Bicalutamide, Clodronate, Epitiostanol, Exemestane, Fadrozole, Flutamide, Formestane, Fulvestrant, Letrozole, Mepitiostane, Nilutamide, Tamoxifen, Toremifene, Trilostane, Krestin, Lentinan, Picibanil, Procodazole, Sizofiran, Ukrain, Virulizin, Alitretinoin, Amsacrine, Bexarotene, Docetaxel, Irinotecan, Miltefosine, Mitoxantrone, Nitracrine, Bortezomib, Paclitaxel, Porfimer, Razoxane, Sobuzoxane, Teniposide, Topotecan, Vindesine, Vinorelbine, Geftinib, Imatinib, Bleomycin, Megestrol, Lenograstim, and mixtures thereof.

z) ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS

Aceclofenac, Diclofenac, Ketorolac, Meloxicam, Naproxen, Piketoprofen, Acemetacin, Alclofenac, Amfenac, Ampiroxicam, Azapropazone, Bufexamac, Butibufen, Carprofen, Chondroitin, Cinmetacin, Clidanac, Dexketoprofen, Diphenpyramide, Droxicam, Emorfazone, Enfenamic Acid, Epirizole, Etersalate, Fenbufen, Fentiazac, Feprazone, Flunoxaprofen, Flurbiprofen, Guaimesal, Ibuproxam, Indometacin, Ketoprofen, Lonazolac, Mabuprofen, Nabumetone, Nimesulide, Oxametacin, Parsalmide, Perisoxal, Piroxicam, Pranoprofen, Proglumetacin, Proquazone, Proticinic acid, Sulindac, Talniflumate, Tolfenamic Acid, Tolmetin, Zaltoprofen, Benzydamine, Etofenamate, Felbinac, Fepradinol, Idocrilamide, Loteprednol, Vessiflex, Glucosaline, Celecoxib, Hyaluronic Acid, Meclofenamate, Piproxen, Tenoxicam, Valdecoxib, Etoricoxib, Rofecoxib, and mixtures thereof.

aa) BISPHOSPHONATES

Risedronate, Tiludronate, Clodronate, Pamidronate, Etidronate, Alendronate,

Zoledronate, Cimadronate, Neridronate, Olpadronate, Minodronate, Ibandronate, and mixtures thereof.

bb) ANALGESICS

Acetylsalicylic Acid, Paracetamol, Codeine, Dihydrocodeine, Dexibuprofen, Alminoprofen, Carbasalate, Desflurane, Diflunisal, Enflurane, Etomidate, Floctafenine, Fosfosal, Isoflurane, Isonixin, Ketorolac, Lornoxicam, Clonixinate, Midazolam, Mofezolac, Naproxen, Nefopam, Propofol, Rimazolium, Rofecoxib, Ropivacaine, Sevoflurane, Parecoxib, Propacetamol, Zaltoprofen, Acemetacin, Sulindac, Indometacin, Mefenamic Acid, Ketoprofen, Diclofenac, Piroxicam, Flupirtine, Mofezolac, Ibuprofen, Fenoprofen, Flurbiprofen, Amtolmentin, Fepradinol, Celecoxib, Valdecoxib, Etoricoxib, Fluproquazon, Nefopam, Asthaxantin, and mixtures thereof.

cc) ANTIMIGRAINE PREPARATIONS

Almotriptan, Propofol, Gabapentin, Zonisamide, Lisinopril, Valproate, Pirprofen, Indoramin, Lidocain, Metoprolol, Ergotamine, Cyproheptadine, Propranolol, Pizotifen, Flunarizine, Nadolol, Metergoline, Ketoprofen, Methysergide, Buclizine, Timolol, Tiaspirone, Topiramate, Somatostatin, Etiracetam, Cinnarizine, Dihydroergotamine, Feverfew, Dronabinol, Dotarizine, Lomerizine, Ibuprofen, Sumatriptan, Naratriptan, Donepezil, Zolmatriptan, Naproxen, Rizatriptan, Montelukast, Frovatriptan, Botulinum Toxin, Alniditan, Avitriptan, Eletriptan, Metoclopramide, Targinine, Aminophylline, Tolfenamic Acid, Isometheptene, and mixtures thereof.

dd) ANTIEPILEPTICS

Phenobarbital, Clonazepam, Felbamate, Fosphentoin, Gabapentin, Lamotrigine, Levetiracetam, Oxcarbazepine, Tiagabine, Topiramate, Valproate, Vigabatrin, Zonisamide, Milacemide, Denzimol, Bretazenil, Eterobarb, Diazepam, Chlormethiazole, Clonazepam, Clobazam, Mefobarbital, Mephenytoin, Primidone,

Acetazolamide, Valpromide, Ralitoline, Fengabine, Licarbazepine, Lorazepam, Antiepilepsirine, Rufinamide, Zaleplon, Abecamil, Losigamone, Selfotel, Midafotel, Remacemide, Carbamazepine, Ethosuximide, Metsuximide, Retigabine, Valnoctamide, and mixtures thereof.

ee) ANTIPSYCHOYTICS

Haloperidol, Sulpiride, Blonanserin, Spiperone, Rimcazole, Isofloxythepin, Remoxipride, Emonapride, Bretazenil, Zuclopenthixol, Veralipride, Bromperidol, Droperidol, Trifluoperazine, Bromazepam, Levopromazine, Fluopromazine, Perphenazine, Thioridazine, Chlorprothixene, Fluphenazine, Periciazine, Tiotixene, Flupentixol, Benperidol, Fluspirilene, Pimozide, Clozapine, Pipotiazine, Loxapine, Tiapride, Zotepine, Sultopride, Lithium Carbonate, Asenapine, Tiaspirone, Ritanserin, Tandospirone, Amperozide, Clospipramine, Nalmefene, Prochlorperazine, Amisulpride, Levosulpriride, Risperidone, Promazine, Perospirone, Aripiprazole, Chlorpromazine, Carpipramine, Iloperidone, Remoxepride, Carbamazepine, Olanzapine, Quetiapine, Ziprasidone, Valproate, Azaperone, Cyamemazine, Timiperone, Bifeprunox, and mixtures thereof.

ff) ANXIOLYTICS

Diazepam, Clorazepate, Pyridoxine, Sulpiride, Lorazepam, Phenobarbital, Meprobamate, Buspirone, Suriclone, Citalopram, Brotizolam, Adinazolam, Etizolam, Bretazenil, Medicar, Enciprazine, Loflazepate, Propranolol, Chlordiazepoxide, Hydroxyzine, Trifluoperazine, Oxazepam, Medazepam, Clonazepam, Oxprenolol, Bromazepam, Clobazam, Nordazepam, Ketazolam, Halazepam, Alprozolam, Fluphenazine, Chlorimipramine, Venlafaxine, Ritanserin, Ipsapirone, Tandospirone, Buspirone, Pazinaclone, Flesinoxan, Fluoxetine, Selfotel, Zatosetron, Pagoclone, Carpipramine, Sunepitron, Sertraline, Paroxetine, Cyclobenzaprine, Cyamemazine, Valnoctamide, Clotiazepam, and mixtures thereof.

gg) ANTIDEPRESSANTS

Citalopram, Venlafaxine, Atomoxetine, Clopradone, Binedaline, Sertraline, Femoxetine, Oxaprotiline, Viqualine, Clovoxamine, Milacemide, Brofaromine, Cianopramine, Moclobemide, Midalcipran, Adinazolam, Nefazodone, Azamianserin, Reboxetine, Tianeptine, Toloxatone, Fluvoxamine, Amitriptyline, Imipramine, Trifluoperazine, Phenelzine, Fluphenazine, Flupentixol, Isocarboxazid, Tranylcypromine, Trimipramine, Desipramine, Opipramol, Nortriptyline, Protriptyline, Doxepin, Lithium Carbonate, Chlorimipramine, Dosulepin, Trazodone, Butriptyline, Viloxazine, Maprotiline, Amoxapine, Lofepramine, Bupropion, Ritanserin, Doconexent, Paroxetine, Ipsapirone, Fengabine, Tandospirone, Setiptiline, Amfebutamone, Lazabemide, Flesinoxan, Adrafinil, Ademetionine, Modafinil, Litoxetine, Fluoxetine, Ceronapril, Cericlamine, Beloxepin, Sunepitron, Agomelatine, Aprepitant, Amineptine, Nomifensine, Chromium Picolinate, and mixtures thereof.

hh) TREATMENT OF ALCOHOL DEPENDANCE

Acamprosate, Vigabatrin, Diazepam, Disulfiram, Ritanserin, Naltrexon, Nalmefene, Carbamazepine, Hydroxybutyrate, Nitrefazole, Metadoxine, and mixtures thereof.

ii) NASAL DECONGESTANTS

Pseudoephedrine, Fluticasone, Indanazoline, Tinazoline, Ipratropium, and mixtures thereof.

jj) DRUGS FOR ASTHMA/OBSTRUCTIVE AIRWAYS DISEASES

Salmeterol, Fenoterol, Ipratropium, Fluticasone, Beclometasone, Flutropium, Talniflumate, Terbutaline, Oxitropium, Rolipram, Seratrodast, Pranlukast, Formoterol, Albuterol, Salbutamol, Midesteine, Tiotropium, Sibenadet, Roflumilast, Aminophylline, Budesonide, Almitrine, Glycopyrrolate, Bambuterol, Mabuterol, Procaterol, Tulobuterol, Rimiterol, Reproterol, Pirbuterol, Daltroban, Ramatroban, Tomelukast, Ibudilast, Pobilukast, Zafirlukast, Montelukast, Methylprednisolone, Dexamethasone, Triamcinolone, Tipredane, Mometasone, Loteprednol, Flunisolide, Hydrocortisone and mixtures thereof.

kk) EXPECTORANTS OR COUGH SUPPRESSANTS

Carbocisteine, Citiolone, Dropropizine, Cloperastine, Ozagrel, Nesosteine, Levodropropizine, Cistinexine, Dextromethorphan, Guaimesal, Nepinalone, Fudosteine, Quinidine, Hydrocodone, Noscapine, Chlorpheniramine and mixtures thereof.

ll) ANTIHISTAMINES FOR SYSTEMIC USE

Terfenadine, Ebastine, Dexchlorpheniramine, Azelastine, Acrivastine, Emedastine, Loratadine, Picumast, Diphenhydramine, Promethazine, Fenclozine, Levocabastine, Desloratadine, Cinnarizine, Setastine, Tagorizine, Mizolastine, Cetirizine, Tazifylline, Epinastine, Olopatadine, Bepotastine, Rupatadine, Norastemizol, Triprolidine, Fexofenadine, Ketotifen, Azatadine, Clemastine, Brompheniramine, and mixtures thereof.

mm) BUCAL ANTISEPTICS

Chlorhexidine, Chloramine-T, Benzalkonium Chloride, and mixtures thereof.

nn) OTHERS

Sulfamethoxazole, Centella, Calcium Folinate, Palmidrol, Thiomucase, Glucomannan, Leucocianidol, Bacterial Lysate, Spagul, and mixtures thereof.

It is preferred that active substance which can be present in the compositions according to the invention is selected from the group consisting of non-lipophilic active substances. The preferred pharmaceutically active substances are antacid compounds. The preferred antacids for use in the invention are generally carbonate or hydroxycarbonate salts of calcium, magnesium, aluminium, or bismuth and combinations thereof, and are generally very water insoluble. Other antacids such as sodium bicarbonate, calcium bicarbonate, and other carbonates, silicates, and phosphates are included in this invention. Preferred antacids are aluminium and magnesium antacids, such as, for example, aluminium hydroxide and magnesium hydroxide and also preferred are crystalline aluminium magnesium hydroxycarbonates

or sulphates such as hydrotalcite, magaldrate and almagate. Almagate is particularly preferred. Mixtures of antacid compounds may be used if desired. When antiacids are used as pharmaceutically active substances they are present in amounts ranging from 5 to 50% by weight of the composition, preferably, between 10 and 45% by weight of the composition, more preferably between 20 and 35% by weight of the composition.

The compositions of the present invention preferably comprise water, more preferably at least 1 % wt. water, and do not comprise edible gums.

The present invention relates also to a process for producing non-tabletted, individually dosed administration forms comprising the steps of: (a) forming a composition comprising at least one pharmaceutically active substance dispersed or dissolved within a matrix material comprising a mixture of gelatine, at least one stabilising agent and at least one water-soluble alcohol and/or water as a solvent, which is plastic at elevated temperature, and keeping such composition above 37° C in a heating tank, (b) transferring the composition, when it is fluid into a heated dosing apparatus, (c) discharging the composition onto a shaped substrate, through a controlled mechanism so that a constant quantity of the fluid formulation material is thereby dosed onto the substrate, (d) cooling the composition, wherein the stabilising agent or agents present in the composition is/are selected from the group consisting of esters of glycerine and fatty acids and products resulting from the alcoholysis / esterification reaction of such esters with polyethyleneglycols and has a melting point in the range of 42° C to 63° C; and (e) optionally sealing the substrate containing the composition.

It is an optional embodiment of the present invention that an adhesion-reducing separating agent is placed on the inner surface of a cavity or a blister prior to step (c) of the above-mentioned process. Examples of such adhesion-reducing separating agents are lecithin, talc, starch, vaseline, and fats which are fluid at 25°C.

It is also a preferred embodiment of the present invention that the cavities or blister of the individually dosed administration forms are made of a material selected from PVC (polyvinyl chloride), PVDC (polyvinylidene chloride), PP (polypropylene), Aclar or laminates such as OPA-Aluminium-PVC (oriented polyamide-aluminium-polyvinyl chloride). PVC is particularly preferred.(in full)

The manufacturing processes described and claimed in European patent application number 0 250 578, which are explicitly incorporated by reference, are modified by the addition of the stabilising agent to the composition to be processed and constitute in this modified form particular preferred embodiments of the process under the present invention.

In another aspect the present invention relates to the use of at least one stabilising agent selected from the group consisting of (i) esters of glycerine and fatty acids (ii) products resulting from the alcoholysis / esterification reaction of such esters with polyethyleneglycols, and having a melting point in the range of 42° C to 63° C to facilitate the removal from the blisters or cavities where they have been packaged, of compositions comprising pharmaceutically active substances dispersed or dissolved within a matrix material comprising a mixture of gelatine and at least one water-soluble alcohol and/or water as a solvent, which composition is plastic at elevated temperature.

As used herein the term "plastic at elevated temperature" is meant to designate a composition which can be molded at temperatures comprised between 45°C and 120°C and keeps its molded shape after it cools to 20°C.

As used herein "melting point" is meant to designate the temperature at which the very last visible particle of a small substance's column introduced in a capillary melts as described in the European Pharmacopea 2.2.14. A suitable apparatus for this determination is the Melting Point Apparatus B-540 available from Büchi Labortechnik AG.

As used herein the term "non-tabletted administration form" is intended to mean any form which has not been manufactured by using conventional tabletting processes such as the tabletting of granular or powdery compositions in an excentric or rotary press machine.

As used herein the term "edible gum" is intended to mean polysaccharide gums comprising among others gum arabic, gum tragacanth, agar agar, xanthan gum, alginates.

As used herein the term "water-soluble alcohol" is meant to designate a pharmaceutically acceptable, liquid monohydric or polyhydric alcohol which can be mixed with water to form a uniform solution in a quantity of at least 10 volumes of alcohol per 100 volumes of water. Examples of such alcohols are ethanol, n-propanol, iso-propanol, glycerol, propylene glycol, 1,3-butylene glycol and polyethylene glycols having a molecular weight comprised between 100 and 600 Dalton.

REMOVAL FROM BLISTER TEST

The compositions to be tested are manufactured according to the process described in example 1 and dosed into cylindrical cavities of circular cross-section having a diameter of 25 mm of a blister packaging made of PVC. The blister is thermo-sealed with an aluminium foil.

The blisters are then stored in a climatic chamber at 40°C and 75% relative humidity for 10 weeks. After this period they are left at 25°C and 60% relative humidity for 24 hours.

For each product to be tested a panel consisting of 5 expert panellists is given 5 samples of the formulation each, and the panellists are asked to remove the composition from the blister where it is packaged by pressing with the thumb on the

plastic wall of the cavity until the composition is expelled from the cavity through the aluminium foil. After the composition has been expelled the remaining aluminium sealing film is removed and the plastic cavity is visually inspected. The panellist are asked to give a sample the rating "Failed" if residues exceeding 0,5 mm in any dimension can be seen in the empty cavity. Otherwise the rating "Passed" must be assigned.

EXAMPLES

Example 1

2060,8 g of a 85% solution of glycerine in water are heated in an Brweka SG3W reactor to 65-75 °C. 288 g of pig skin gelatine of 240 degrees Bloom are slowly and continuously added during approximately 4 minutes until complete solubilisation has taken place. The mixture is stirred for 10 additional minutes. 48 g of lecithin are incorporated and the mixture stirred for 10 minutes. 800 g of almagate are then slowly and continuously added during approximately 15 minutes and the mixture stirred for 20 additional minutes at 75-80°C. 3,2 gr of flavour are successively incorporated and the solution stirred for 5 minutes. 4 g of the molten composition are dosed into the cylindrical cavities of circular cross-section having a diameter of 25 mm of a blister packaging made of PVC. The blister is thermo-sealed with an aluminum foil.

The composition of each individual cavity is as follows:

Ingredient	% wt.
Almagate	2500
Gelatine	900
Glycerine (100%)	5474

Water	966
Lecithin	150
Flavour	10

Examples 2 to 7

Compositions 2 to 7 were manufactured following the process described in example 1 modified in that 1900,8 gr of the glycerine solution were used, and in that 160 g. of a stabilising agent were added after the complete solubilisation of gelatine had taken place and before the addition of lecithin. After the solubilisation of gelatine the mixture was stirred for 20 minutes and the temperature of the reactor was raised to 75-80°C and 160 g of the stabilising agent were slowly and continuously added during approximately 5 minutes.

The following compositions were manufactured following this process:

Example	Stabilising agent (Tradename)	Stabilising agent (Chemical nature)	Melting range (°C)
2	Cutine HR	Hydrogenated castor oil	87-88
3	Compritol 888 ATO	Glyceryl behenate	71,4-72,2
4	Akofine NF	Hydrogenated cottonseed oil	63,4-63,9
5	Estol 3745 GDS T2	Glyceryl diestearate	59,0-59,7

		80	
6	Gelucire 50/13	Stearoyl macrogol-32 glycerides	50,3-51,0
7	Gelucire 44/14	Lauryl macrogol-32 glycerides	43,6-44,2

To evaluate the contribution of the stabilising agent, the compositions of examples 1 to 7 were subjected to the "removal from blister test" described above with the following results:

Example	Removal from Blister Test
1	Failed
2	Failed
3	Failed
4	Failed
5	Passed
6	Passed
7	Passed

CLAIMS

1. Non-tabletted, individually dosed administration forms comprising a composition of at least one pharmaceutically active substance dissolved or dispersed within a matrix material comprising a mixture of at least 0,2% by weight of a gelatine, at least one stabilising agent and at least one water-soluble alcohol and/or water as a solvent, which composition is plastic at elevated temperature, characterised in that

a. the stabilising agent is selected from the group consisting of (i) esters of glycerine and fatty acids; (ii) products resulting from the alcoholysis / esterification reaction of such esters of glycerine and fatty acids with polyethylenglycols; and

b. in that the stabilising agent has a melting point in the range of 42° C to 63° C

c. in that water is present in an amount not greater than 46% by weight of the composition.

2. Non-tabletted, individually dosed administration forms according to claim 1 characterised in that they are packaged in blisters or cavities shaped from films.

3. Non-tabletted, individually dosed administration forms according to any preceding claim characterised in that they comprisesan antacid.

4. Non-tabletted, individually dosed administration forms according to any preceding claim characterised in that they comprise at least 10% by weight of the composition of at least one water-soluble alcohol and/or water as a solvent.

5. Non-tabletted, individually dosed administration forms according to any preceding claim characterised in that it comprises water, preferably in an amount exceeding 1 % wt. of the overall composition.

6. Non-tabletted, individually dosed administration forms according to any preceding claim characterised in that the composition does not comprise edible gums.

7. A process for producing non-tabletted, individually dosed administration forms comprising the following steps:

forming a composition comprising at least one pharmaceutically active substance dispersed or dissolved within a matrix material comprising a mixture comprising at least 0,2% by weight of a gelatine, at least one stabilising agent and at least one water-soluble alcohol and/or water as a solvent, which is plastic at elevated temperature and, keeping such composition above 37° C in a heating tank.

transferring the composition, when it is fluid into a heated dosing apparatus

discharging the composition onto a shaped substrate, through a controlled mechanism so that a constant quantity of the fluid formulation material is thereby dosed onto the substrate

cooling the composition

optionally sealing the substrate containing the composition.

wherein water is present in an amount not greater than 46% by weight of the composition and the at least one stabilising agent is selected from the group consisting of (i) esters of glycerine and fatty acids; (ii) products resulting from the alcoholysis / esterification reaction of such esters with polyethyleneglycols, and has a melting point in the range of 42° C to 63 °C.

8. A process according to claim 7 characterised in that the pharmaceutically active substances comprise an antacid.

9. A process according to anyone of claims 7 or 8 characterised in that the composition comprises water, preferably in an amount exceeding 1% wt. of the

overall composition.

10. A process according to anyone of claims 7 to 9 characterised in that the composition does not comprise edible gums.

11. Process according to anyone of claims 7 to 10, wherein the cavity or blister comprises a material selected from the group consisting of PVC, PVDC, PP, Aclar or laminates such as OPA-Aluminium-PVC.

12. Non-tabletted, individually dosed administration forms obtainable by the process of claims 7 to 11

13. Use of at least one stabilising agent selected from the group consisting of (i) esters of glycerine and fatty acids (ii) products resulting from the alcoholysis / esterification reaction of such esters with polyethyleneglycols, having a melting point in the range of 42° C to 63° C to facilitate the removal from the blisters or cavities where they have been packaged, of compositions comprising at least one pharmaceutically active substance dispersed or dissolved within a matrix material comprising a mixture of gelatine and at least one water-soluble alcohol and/or water as a solvent, which composition is plastic at elevated temperature.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/002513

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 078 215 A (RHONE POULENC SANTE) 4 May 1983 (1983-05-04) page 1, line 29 - page 2, line 9 examples 7,8	1-12
X	US 6 060 078 A (YOUNG WON LEE) 9 May 2000 (2000-05-09) claims 1,3,4,6,9	1-6
Y	column 5; example 3	3,8
X	WO 02/064109 A (GW PHARMA) 22 August 2002 (2002-08-22)	1,2,4-7, 9-12
Y	claims 1,3,5-7	3,8
A	page 6, line 7 - line 11 page 13, line 19 - line 25 page 14; table 2 page 38; example 2	13

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	VON EGGELKRAUT, S

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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